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DATE: Monday, November 04, 2002

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L7	L6 and enantiomeric	56	L7
L6	lactamase and hydrolysis	2137	L6
L5	L3 and hydrolysis	32	L5
L4	L3 and lactam	3	L4
L3	rhodococcus equi	148	L3
L2	enzymic and resolution and racemates and equi and rhodococcus	0	L2
L1	azabicyclo and enzymic and resolution and racemates and equi and rhodococcus	0	L1

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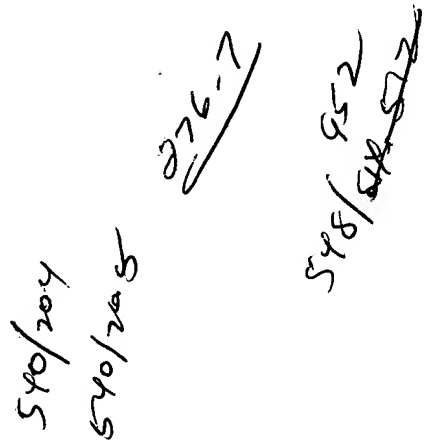

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Class 540 ORGANIC COMPOUNDS -- PART OF THE CLASS 532-570 SERIES

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This Class 540 is considered to be an integral part of Class 260 (see the Class 260 schedule for the position of this Class in schedule hierarchy). This Class retains all pertinent definitions and class lines of Class 260.

ORGANIC COMPOUNDS (CLASS 532, SUBCLASS 1)

1	. HETEROCYCLIC CARBON COMPOUNDS CONTAINING A HETERO RING HAVING CHALCOGEN (I.E., OXYGEN, SULFUR, SELENIUM OR TELLURIUM) OR NITROGEN AS THE ONLY RING HETERO ATOMS
2	.. Cyclopentanohydrophenanthrene ring system containing
3	... Heavy metal or aluminum containing
4	... Boron or silicon containing
5	... Phosphorus attached directly or indirectly to the cyclopentanohydrophenanthrene ring system by nonionic bonding
6	... Spiro
7	.... Plural spiro atoms
8	..... The cyclopentanohydrophenanthrene ring system is part of a polycyclo ring system having at least five cyclos
9	..... Nitrogen containing hetero ring as one of the cyclos of the polycyclo ring system
10	..... The cyclopentanohydrophenanthrene ring system shares spiro atoms with two hetero rings, each of which contains two oxygens (e.g., 3,17-bis-ketals, etc.)
11	..... The cyclopentanohydrophenanthrene ring system shares a spiro atom with a lactone ring (i.e., -C(=X)-O- is part of the ring, wherein X is chalcogen)
12	..... Plural oxygens in both rings which share a spiro atom (e.g., 17,20;20,21 bismethylenedioxy-pregnanes, etc.)
13	..... Nitrogen, sulfur, cyano or -C(=X)-, wherein X is chalcogen, bonded directly to the cyclopentanohydrophenanthrene ring system
14	..... Halogen attached directly or indirectly to the cyclopentanohydrophenanthrene ring system by acyclic nonionic bonding
15	.... The cyclopentanohydrophenanthrene ring system is part of a polycyclo ring system having at least five cyclos
16	..... Hetero ring is one of the cyclos of the polycyclo ring system
17	..... The hetero ring is five-membered, consisting of one oxygen and four carbons, and shares the spiro atom with a six-membered oxygen containing hetero ring (e.g., sapogenins, etc.)
18	..... Purification or recovery
19	..... Chalcogen bonded directly at the 12-position of the cyclopentanohydrophenanthrene ring system (e.g., hecogenin, etc.)
20	..... Chalcogen bonded directly at the 11-position of the cyclopentanohydrophenanthrene ring system
21	..... Chalcogen bonded directly at the 7-position of the cyclopentanohydrophenanthrene ring system
22	..... Halogen, cyano, nitrogen or sulfur bonded directly to the cyclopentanohydrophenanthrene ring system
23	..... The spiro atom is the 17-position carbon of the cyclopentanohydrophenanthrene ring system
24	..... The hetero ring shares the 11,12,13-positions of the cyclopentanohydrophenanthrene ring system (i.e., bridged; e.g., 11,18-oxido steroids, etc.)

25 ..... The hetero ring is three-membered consisting of one oxygen and two carbons (e.g., oxirane, etc.)
26 ..... The hetero ring shares the 5,6-positions of the cyclopentanohydrophenanthrene ring system
27 ..... The hetero ring contains two chalcogens which are bonded directly at the 16 and 17-positions of the cyclopentanohydrophenanthrene ring system
28 .... The spiro includes the cyclopentanohydrophenanthrene ring system and a hetero ring
29 ..... Nitrogen in the spiro hetero ring
30 ..... Sulfur in the spiro hetero ring
31 ..... Plural oxygens in the spiro hetero ring
32 ..... The A ring is a benzene ring
33 ..... Chalcogen bonded directly to the spiro hetero ring
34 ..... The spiro hetero ring shares the 3-position carbon of the cyclopentanohydrophenanthrene ring system
35 ..... Halogen bonded directly to the cyclopentanohydrophenanthrene ring system
36 ..... Nitrogen attached directly or indirectly to the cyclopentanohydrophenanthrene ring system by nonionic bonding
37 ..... Plural cyclic ketal rings containing (e.g., 3,20-bis-ketals, etc.)
38 ..... Chalcogen bonded directly at the 11-position of the cyclopentanohydrophenanthrene ring system
39 ..... The cyclopentanohydrophenanthrene ring system is fully saturated
40 ..... Carbon chain having carbon-to-carbon unsaturation bonded directly at the 17 position of the cyclopentanohydrophenanthrene ring system
41 ..... The spiro hetero ring contains -C(=X)-O-, wherein X is chalcogen, as part of the ring (e.g., spiro-lactones, etc.)
42 ..... Sulfur bonded directly to the cyclopentanohydrophenanthrene ring system
43 ..... Chalcogen bonded directly at the 11-position of the cyclopentanohydrophenanthrene ring system
44 ..... Chalcogen, halogen, or nitrogen attached indirectly to the cyclopentanohydrophenanthrene ring system by acyclic nonionic bonding
45 ..... The spiro hetero ring is four-membered consisting of one oxygen and three carbons
46 ..... The spiro hetero ring is three-membered consisting of one oxygen and two carbons (e.g., oxirane, etc.)
47 ... The cyclopentanohydrophenanthrene ring system is part of a polycyclo ring system having at least five cyclos
48 .... Hetero ring is one of the cyclos of the polycyclo ring system
49 ..... The hetero ring contains nitrogen
50 ..... Plural nitrogens in the hetero ring
51 ..... The hetero ring is five-membered
52 ..... The hetero ring consists of two nitrogens and three carbons and is ortho fused to the A ring
53 ..... Having -C(=X)-, wherein X is chalcogen, bonded directly at the 17-position of the cyclopentanohydrophenanthrene ring system
54 ..... The hetero ring consists of two nitrogens and three carbons and is ortho fused to the D ring
55 ..... Chalcogen in the hetero ring
56 ..... The hetero ring is five-membered
57 ..... The hetero ring is ortho-fused to the A ring
58 ..... The hetero ring is five-membered
59 ..... The hetero ring contains sulfur
60 ..... The hetero ring is a cyclic anhydride (i.e., containing -C(=X)-O-C(=Y)- as part of the ring, wherein X and Y are chalcogen; e.g., 5,8-maleic anhydride adduct of 5,7,9(11)-pregnatrien-3,20-di-one, etc.)
61 ..... The hetero ring contains plural oxygens
62 ..... Two of the cyclos share at least three ring members or a ring carbon is shared by three of the cyclos (e.g., bridged, peri-fused, etc.)

63 ..... The hetero ring is ortho-fused to the D ring
64 ..... At least six cyclos in the polycyclo ring system
65 ..... Nitrogen or acyclic chalcogen bonded directly to the hetero ring (e.g., cyclic carbonates, etc.)
66 ..... The A ring is a benzene ring
67 ..... Sulfur or nitrogen attached directly or indirectly to the cyclopentanohydrophenanthrene ring system by acyclic nonionic bonding
68 ..... Halogen attached indirectly to the cyclopentanohydrophenanthrene ring system by acyclic nonionic bonding
69 ..... Halogen bonded directly to the cyclopentanohydrophenanthrene ring system
70 ..... Oxygen bonded directly at the 11-position of the cyclopentanohydrophenanthrene ring system
71 ..... Oxygen attached directly to the B ring or indirectly to the A or B ring by acyclic nonionic bonding
72 ..... The hetero ring is a lactone (i.e., containing -C(=X)-O- as part of the ring, wherein X is chalcogen)
73 ..... The lactone ring shares at least three ring members with one other cyclo of the polycylo ring system (i.e., bridged)
74 ..... The lactone ring shares the 11,12,13-positions of the cyclopentanohydrophenanthrene ring system (e.g., 11, 18-lactones, etc.)
75 ..... The lactone ring shares a ring carbon with two other cyclos of the polycyclo ring system (e.g., peri-fused, etc.)
76 ..... The hetero ring is three-membered consisting of one oxygen and two carbons (e.g., oxirane, etc.)
77 ..... The polycyclo ring system contains plural oxirane rings
78 ..... The hetero ring shares the 1,2-positions of the cyclopentanohydrophenanthrene ring system
79 ..... The hetero ring shares the 4,5-positions of the cyclopentanohydrophenanthrene ring system
80 ..... The hetero ring shares the 5,6-positions of the cyclopentanohydrophenanthrene ring system
81 ..... The hetero ring shares the 6,7-positions of the cyclopentanohydrophenanthrene ring system
82 ..... The hetero ring shares the 11,12-positions of the cyclopentanohydrophenanthrene ring system
83 ..... The hetero ring shares the 14,15-positions of the cyclopentanohydrophenanthrene ring system
84 ..... The hetero ring shares the 16,17-positions of the cyclopentanohydrophenanthrene ring system
85 ..... Halogen bonded directly to the cyclopentanohydrophenanthrene ring system
86 ..... Saturated A ring
87 ..... The hetero ring shares the 9,11-positions of the cyclopentanohydrophenanthrene ring system
88 ..... Halogen bonded directly to the cyclopentanohydrophenanthrene ring system
89 ..... Having -C(=X)-, wherein X is chalcogen, bonded directly to the cyclopentanohydrophenanthrene ring system
90 ..... The hetero ring shares at least three ring members with one other cyclo of the polycyclo ring system (i.e., bridged)
91 ..... Bridge consisting of oxygen and carbon between the 6- and 10-positions of the cyclopentanohydrophenanthrene ring system (e.g., 6,19-oxido steroids, etc.)
92 ..... Bridge consisting of oxygen and carbon between the 11- and 13-positions of the cyclopentanohydrophenanthrene ring system (e.g., 11,18-oxido steroids, etc.)
93 ..... The hetero ring shares a ring carbon with two other cyclos of the polycyclo ring system (e.g., peri-fused, etc.)
94 ... Hetero ring attached directly to the cyclopentanohydrophenanthrene ring system by nonionic bonding
95 .... The hetero ring contains nitrogen

96 ..... Plural nitrogen containing hetero rings bonded directly to the cyclopentanohydrophenanthrene ring system
97 ..... The hetero ring is bonded directly at the 3-position of the cyclopentanohydrophenanthrene ring system
98 ..... The A ring is a benzene ring
99 ..... Halogen bonded directly to the cyclopentanohydrophenanthrene ring system
100 .... The hetero ring contains plural chalcogens
101 ..... The hetero ring and acyclic chalcogen are both bonded directly at the 17 position of the cyclopentanohydrophenanthrene ring system
102 .... The hetero ring contains -C(=X)-O-, wherein X is chalcogen, as part of the ring (e.g., lactones, etc.)
103 ..... Additional chalcogen, cyano, or -C(=X)-, wherein X is chalcogen, bonded directly to the hetero ring
104 ..... Nitrogen or sulfur attached directly or indirectly to the cyclopentanohydrophenanthrene ring system by nonionic bonding
105 ..... Chalcogen bonded directly at the 14-position of the cyclopentanohydrophenanthrene ring system or double bond in the D ring (e.g., cardenolides, etc.)
106 ... Nitrogen attached directly to the cyclopentanohydrophenanthrene ring system by nonionic bonding
107 ... Nitrogen containing hetero ring attached indirectly to the cyclopentanohydrophenanthrene ring system by nonionic bonding
108 .... The hetero ring is five-membered and has plural hetero atoms
109 .... The hetero ring is in the 17-position substituent of the cyclopentanohydrophenanthrene ring system
110 ..... The hetero ring is bonded directly to a -C(=X)- group, wherein X is chalcogen
111 ..... Having -C(=X)-, wherein X is chalcogen, bonded directly at the 17-position of the cyclopentanohydrophenanthrene ring system
112 ..... Chalcogen or nitrogen in chain between the hetero ring and the cyclopentanohydrophenanthrene ring system
113 .... Chalcogen in chain between the hetero ring and the cyclopentanohydrophenanthrene ring system
114 ... Oxygen containing hetero ring attached indirectly to the cyclopentanohydrophenanthrene ring system by nonionic bonding
115 .... The hetero ring contains -C(=X)-O-, wherein X is chalcogen, as part of the ring (e.g., lactones, etc.)
116 .... Additional hetero atom in the oxygen containing hetero ring
117 .... The A ring is a benzene ring
118 .... The hetero ring is bonded directly to chalcogen which is bonded directly to the cyclopentanohydrophenanthrene ring system
119 ..... The chalcogen is bonded directly at the 17-position of the cyclopentanohydrophenanthrene ring system
120 ... Chalcogen attached indirectly to the cyclopentanohydrophenanthrene ring system by nonionic bonding
121 .. Azaporphyrins
122 ... Phthalocyanines
123 .... Hetero ring attached directly or indirectly to the phthalocyanine ring system by nonionic bonding
124 ..... The hetero ring is six-membered having nitrogen as a ring member
125 ..... Plural hetero atoms in the six-membered hetero ring
126 ..... Triazines (including hydrogenated)
127 ..... The hetero ring is five-membered having plural hetero atoms, at least one of which is nitrogen
128 .... Boron, germanium, phosphorus or silicon containing
129 .... Having -C(=X)-, wherein X is chalcogen, bonded directly to ring carbon of the phthalocyanine ring system (e.g., tetracarboxy copper phthalocyanine, etc.)

130	.... Having -C(=X)-, wherein X is chalcogen, attached indirectly to ring carbon of the phthalocyanine ring system by nonionic bonding (e.g., phthalocyanine acetic acids, etc.)
131	.... Sulfonyl bonded directly to ring carbon of the phthalocyanine ring system
132	..... Chalcogen bonded directly to the sulfonyl group
133	..... Nitrogen bonded directly to the sulfonyl group
134	..... Additional nitrogen in the sulfonyl containing substituent
135	.... Nitrogen attached indirectly to ring carbon of the phthalocyanine ring system by acyclic nonionic bonding
136	.... Halogen bonded directly to ring carbon of the phthalocyanine ring system
137	..... At least eight halogens bonded directly to ring carbons of the phthalocyanine ring system
138	..... Processes of halogenating the phthalocyanine ring system
139	.... Metal containing
140	..... Heavy metal or aluminum containing
141	..... Specified crystalline form or processes of milling (e.g., alpha crystalline form, ball milling, acid milling, etc.)
142	..... Processes of forming the phthalocyanine ring system
143	..... From reactant which contains plural cyano groups (e.g., preparing from phthalonitrile, etc.)
144	..... From reactant which contains plural carbonyl groups (e.g., preparing from phthalic anhydride, etc.)
145	.. Porphyrins (including hydrogenated; e.g., chlorophyll, etc.)
200	.. Hetero ring is four-membered containing nitrogen and having chalcogen double bonded directly to a ring carbon which is adjacent to the ring nitrogen
201	... Heavy metal containing
202	... Plural hetero atoms in the hetero ring
203	... Polycyclo ring system containing the hetero ring as one of the cyclos
204	.... The ring nitrogen is shared by a ring containing at least seven members
205	.... The ring nitrogen is shared by a six-membered ring
214	..... The six-membered ring contains sulfur
215	..... 1-thia-5-aza-bicyclo(4.2.0)octane (including unsaturated; e.g., cepham, etc.)
216	..... The 1-thia-5-aza-bicyclo(4.2.0)oct-ane is part of a polycyclo ring system having at least three cyclos
217	..... Double bond between the 2,3-positions of the bicyclo ring system (e.g., 2 cephem, etc.)
218	..... Ring expansion to produce the bicyclo ring system
219	..... 7-amino cephalosporanic acid per se or salt thereof (i.e., 7-ACA or salt thereof)
220	..... Purification or recovery
221	..... 7,7-disubstituted
222	..... Additional hetero ring containing
223	..... 2- or 4-position substituent contains hetero ring
224	..... 3-position substituent contains a pyridine ring (e.g., quinoline, thienopyridine, lutidines, etc.)
225	..... 7-position substituent contains hetero ring
226	..... 3-position substituent contains sulfur
227	..... 7-position substituent contains hetero ring
228	..... Alkyl, hydroxyalkyl, alkoxyalkyl or alkanoyloxyalkyl bonded directly to 3 position
229	..... Sulfur containing substituent
230	..... Alkyl, hydroxyalkyl, alkoxyalkyl or alkanoyloxyalkyl bonded directly to 3 position
300	..... The six-membered ring contains oxygen
301	..... 1-oxa-5-aza-bicyclo(4.2.0)octane (including unsaturated)
302	.... The ring nitrogen is shared by a five-membered ring
303	..... The five-membered ring contains an additional hetero atom
304	..... 1-thia-4-aza-bicyclo(3.2.0)hep-tane (including unsaturated; e.g., penam, etc.)
305	..... The 1-thia-4-aza-bicyclo(3.2.0)hep-tane is part of a polycyclo ring system having at least three cyclos

306 ..... Plural 1-thia-4-aza-bicyclo(3.2.0)hep-tane ring systems attached directly or indirectly to each other by nonionic bonding
307 ..... Spiro
308 ..... The 6-position substituent contains phosphorus attached directly or indirectly to the bicyclo ring system by nonionic bonding
309 ..... Nitrogen containing hetero ring attached directly at the 3-position of the bicyclo ring system
310 ..... Having -C(=X)-, wherein X is chalcogen, bonded directly at the 3-position of the bicyclo ring system
311 ..... Nitrogen or hydrogen bonded directly to the -C(=X)- group
312 ..... Nitrogen bonded directly at the 6-position of the bicyclo ring system
313 ..... The 2-position substituent contains chalcogen, nitrogen or halogen
314 ..... Having -C(=X)-, wherein X is chalcogen, single bonded directly to the nitrogen (e.g., penicillin F, etc.)
315 ..... Processes utilizing penam containing compound
316 ..... Introduction of -C(=X)- group, wherein X is chalcogen, onto nitrogen (e.g., carboxamide formation, etc.)
317 ..... Boron, silicon or phosphorus containing reactant
318 ..... Esterification of the 3-position -C(=X)X- group, wherein the X's may be the same or diverse chalcogens
319 ..... Sulfur-oxidation, epimerization, 6-alkoxylation, de-esterification or reduction
320 ..... Formation of solvate or anhydrous forms, or special crystalline forms
321 ..... Conversion of amine salts to metal salts
322 ..... Purification utilizing solid adsorbent
323 ..... Base salt formation of 3-position -COOH group
324 ..... Extracting solid from solution
325 ..... The nitrogen is part of a hetero ring
326 ..... Chalcogen, -C(=X)-, wherein X is chalcogen, or additional nitrogen bonded directly to the -C(=X)- group
327 ..... Hetero ring or ring system bonded directly to the -C(=X)- group
328 ..... Nitrogen containing ring or ring system attached by carbon or acyclic carbon chain to the -C(=X)- group
329 ..... Polycyclo heterocyclic ring system in 6-position substituent
330 ..... The polycyclo ring system is attached directly to a -C(=X)-NH- group, wherein X is chalcogen and substitution may be made for hydrogen only, which group is between the polycyclo ring system and the 1-thia-4-aza bicyclo(3.2.0)hep-tane
331 ..... Acyclic nitrogen or azide attached indirectly to the -C(=X)- group by acyclic nonionic bonding
332 ..... Having -C(=X)-, wherein X is chalcogen, bonded directly to the nitrogen
333 ..... Hetero ring bonded directly to the -C(=X)- group
334 ..... Chalcogen, additional nitrogen or additional -C(=X)- bonded directly to the -C(=X)- group
335 ..... Additional acyclic nitrogen or acyclic chalcogen in the 6-position substituent
336 ..... The -C(=X)- group, an unsubstituted benzene ring and -NHH bonded directly to the same carbon atom (e.g., ampicillin, etc.)
337 ..... Cycloaliphatic ring in 6-position substituent
338 ..... Benzene or hetero ring in 6-position substituent
339 ..... The ring is bonded directly to the -C(=X)- group
340 ..... Having -C(=X)X-, wherein the X's may be the same or diverse chalcogens, in chain between the ring and the -C(=X)- group
341 ..... Chalcogen in the chain between the ring and the -C(=X)- group
342 ..... Unsubstituted hydrocarbyl chain between the ring and the -C(=X)- group
343 ..... Amine addition salts of 3-position -COOH group
344 ..... Nitrogen containing hetero ring in the cation (i.e., amine moiety)
345 ..... Plural nitrogens in the cation (i.e., amine moiety)
346 ..... Processes
347 ..... Bicyclo ring system which is 1-oxa-4-aza-bicyclo(3.2.0)hep-tane (including unsaturated)

348 ..... Acyclic carbon double bonded directly at the 2-position of the bicyclo ring system
349 ..... Chalcogen attached directly by a single bond to the carbon or to an acyclic carbon chain which contains the carbon
350 ..... The ring system is 4-aza-bicyclo(3.2.0)heptane (including unsaturated) and has sulfur bonded directly at the 2-position
351 ..... Thienamycin per se or salt thereof
352 .... Five-membered hetero ring consisting of one nitrogen, one sulfur and three carbons as one of the cyclos of the polycyclo ring system
353 ..... Double bond between ring members of the five-membered hetero ring
354 ... Additional chalcogen bonded directly to the hetero ring
355 .... The additional chalcogen is bonded directly to the ring nitrogen
356 .... The additional chalcogen is double bonded directly to the hetero ring
357 .... Having -C(=X)-, wherein X is chalcogen, bonded directly to the additional chalcogen
358 .... The additional chalcogen is sulfur which is bonded directly to chalcogen
359 ..... The sulfur is double bonded directly to the chalcogen
360 .... Additional carbon bonded directly to the additional chalcogen
361 ... Halogen attached directly at the 4-position of the hetero ring by nonionic bonding
362 ... The 4-position of the hetero ring is unsubstituted or alkyl substituted only
363 .... Nitrogen bonded directly at the 3-position of the hetero ring
364 ... Nitrogen bonded directly at the 3-position of the hetero ring
450 .. The hetero ring contains at least eight members including nitrogen and carbon
451 ... Chalcogen double bonded directly to a ring carbon of the hetero ring which is adjacent to the ring nitrogen (e.g., laurolactam, etc.)
452 .... Heavy metal, aluminum, boron or silicon containing
453 .... Spiro
454 .... Chalcogen in the hetero ring
455 ..... Polycyclo ring system which contains the hetero ring as one of the cyclos
456 ..... Two of the cyclos share at least three ring members or a ring member is shared by three of the cyclos (e.g., bridged, peri-fused, etc.)
457 ..... A five-membered cyclo of the polycyclo ring system consists of four ring carbons and one ring oxygen (e.g., fused rifamycins, etc.)
458 ..... Tetracyclo ring system which contains the hetero ring as one of the cyclos (e.g., rifamycin S, etc.)
459 ..... Nitrogen, sulfur or halogen attached directly to the tetracyclo ring system by nonionic bonding
460 .... Plural nitrogens in the hetero ring
461 .... Polycyclo ring system which contains the hetero ring as one of the cyclos
462 ..... Oxirane ring is one of the cyclos in the polycyclo ring system (e.g., maytansinol, etc.)
463 .... Nitrogen or additional chalcogen attached directly to the hetero ring by nonionic bonding
464 .... Utilizing oximes, oxime salts, hydroxylamines, hydroxylamine salts or nitrosating agents to form the hetero ring (i.e., formation of the lactam ring)
465 ... Heavy metal or aluminum containing
466 ... Spiro
467 ... The hetero ring contains chalcogen
468 .... Polycyclo ring system which contains the hetero ring as one of the cyclos
469 ..... Plural nitrogens in the hetero ring
470 ... The hetero ring contains plural nitrogens
471 .... Polycyclo ring system which contains the hetero ring as one of the cyclos
472 ..... Two of the cyclos share at least three ring members or a ring member is shared by three of the cyclos (e.g., bridged, peri-fused, etc., toxiferin)
473 ..... Bicyclo ring system which contains the hetero ring as one of the cyclos
474 .... The hetero ring contains at least three nitrogens
475 ..... Nitro bonded directly to ring nitrogen of the hetero ring (e.g., HMX, etc.)
476 ... Polycyclo ring system which contains the hetero ring as one of the cyclos

477 .... Two of the cyclos share at least three ring members or a ring member is shared by three of the cyclos (e.g., bridged, peri-fused, etc.)
478 ..... Containing additional heterocyclic polycyclo ring system having plural ring nitrogens (e.g., vinblastine, vincristine, etc.)
479 .... Tricyclo ring system which contains the hetero ring as one of the cyclos
480 ... Additional hetero ring attached directly or indirectly to the hetero ring by nonionic bonding
481 .... The additional hetero ring is six-membered and contains nitrogen
482 ... Chalcogen or nitrogen attached directly to the hetero ring by nonionic bonding
483 ... Plural nitrogens attached indirectly to the hetero ring by acyclic nonionic bonding
484 .. The hetero ring contains seven members including nitrogen and carbon
485 ... Chalcogen double bonded directly to a ring carbon adjacent to the ring nitrogen (e.g., caprolactam, etc.)
486 .... Heavy metal or aluminum containing
487 .... Silicon or phosphorus attached directly or indirectly to the hetero ring by nonionic bonding
488 .... Chalcogen in the hetero ring
489 ..... Plural nitrogens in the hetero ring
490 ..... Bicyclo ring system having the hetero ring as one of the cyclos
491 ..... The chalcogen and the nitrogen are in the 1,5-positions of the bicyclo ring system (e.g., 1,5-benzothiazepinone, etc.)
492 .... Plural nitrogens in the hetero ring
493 ..... Tetracyclo ring system having the hetero ring as one of the cyclos
494 ..... Nitrogen of the hetero ring is shared by an additional cyclo of the tetracyclo ring system
495 ..... Tricyclo ring system having the hetero ring as one of the cyclos
496 ..... Nitrogen of the hetero ring is shared by an additional cyclo of the tricyclo ring system
497 ..... Additional hetero atom in the additional cyclo of the tricyclo ring system
498 ..... The additional cyclo is five-membered consisting of nitrogen and carbon (e.g., imidazobenzodiazepinones, etc.)
499 ..... The additional cyclo consists of three nitrogens and two carbons (e.g., triazolobenzodiazepinones, etc.)
500 ..... Bicyclo ring system having the hetero ring as one of the cyclos
501 ..... At least three nitrogens in the hetero ring
502 ..... At least three hetero atoms in the bicyclo ring system
503 ..... Chalcogen in the bicyclo ring system
504 ..... The bicyclo ring system is 1,4-benzodiazepine (including hydrogenated)
505 ..... The chalcogen double bonded directly to the hetero ring is sulfur
506 ..... Additional chalcogen bonded directly to ring carbon of the hetero ring
507 ..... The additional chalcogen is bonded directly at the 3-position of the bicyclo ring system
508 ..... Nitrogen or -C(=X)-, wherein X is chalcogen, attached indirectly to the chalcogen by acyclic nonionic bonding
509 ..... Acyclic nitrogen bonded directly to the hetero ring
510 ..... Having -C(=X)-, wherein X is chalcogen, bonded directly to the hetero ring
511 ..... Halogen bonded directly to the hetero ring
512 ..... Chalcogen attached indirectly to nitrogen of the hetero ring by acyclic nonionic bonding
513 ..... Sulfur, -C(=X)-, wherein X is chalcogen, or nitrogen, other than as nitro or nitroso, bonded directly to the carbocyclic ring of the bicyclo ring system
514 ..... Nitrogen in the 1-position substituent of the bicyclo ring system
515 ..... Preparation by cyclizing benzophenones or imine derivatives thereof
516 ..... Preparation from a compound containing a different hetero ring
517 ..... The bicyclo ring system is 1,5-benzodiazepine (including hydrogenated)
518 ..... Additional chalcogen double bonded directly to ring carbon of the hetero ring
519 .... Polycyclo ring system which contains the hetero ring as one of the cyclos

520 ..... Two of the cyclos share at least three ring members or a ring member is shared by three of the cyclos (e.g., bridged, peri-fused, etc.)
521 ..... Plural hetero atoms in the polycyclo ring system
522 ..... Tricyclo ring system which contains the hetero ring as one of the cyclos
523 ..... Bicyclo ring system which contains the hetero ring as one of the cyclos
524 .... Additional hetero ring containing
525 ..... Plural seven-membered hetero rings
526 .... Additional chalcogen bonded directly to the hetero ring
527 .... Nitrogen bonded directly to the hetero ring
528 ..... The nitrogen is bonded additionally only to hydrogen
529 .... Having -C(=X)-, wherein X is chalcogen, bonded directly to the hetero ring
530 .... Halogen bonded directly to the hetero ring
531 .... Chalcogen or nitrogen attached indirectly to the hetero ring by nonionic bonding
532 .... Preparing from a compound containing a hetero ring
533 ..... The hetero ring is a lactam (i.e., -C(=X)-NH- is part of the ring, wherein X is chalcogen and substitution may be made for the hydrogen only)
534 .... Preparing from a compound containing a cycloaliphatic ring
535 ..... The reactant is a cyclic oxime
536 ..... Gas phase rearrangement
537 ..... Acyclic -C(=X)X-, wherein the X's are the same or diverse chalcogens, attached directly to the cycloaliphatic ring by nonionic bonding
538 .... Cyclization to form the hetero ring
539 ..... Reactant contains a cyano group
540 .... Purification or recovery
541 ... Heavy metal or boron containing
542 ... Phosphorus attached directly or indirectly to the hetero ring by nonionic bonding
543 ... Spiro
544 ... The hetero ring contains chalcogen
545 .... Plural nitrogens in the heterocyclic ring
546 .... Polycyclo ring system which contains the hetero ring as one of the cyclos
547 ..... Tricyclo ring system which contains the hetero ring as one of the cyclos
548 ..... At least three ring hetero atoms in the tricyclo ring system
549 ..... Sulfur and nitrogen are bonded directly to each other in the hetero ring
550 ..... The nitrogen of the hetero ring is bonded directly to both remaining rings of the tricyclo ring system (e.g., dibenzo(b,e)(1,4)thiazepine, etc.)
551 ..... Nitrogen bonded directly to ring carbon of the hetero ring
552 ..... Bicyclo ring system which contains the hetero ring as one of the cyclos
553 ... The hetero ring contains plural nitrogens (e.g., 1,3-diazepines, etc.)
554 .... The hetero ring contains at least three nitrogens
555 .... Polycyclo ring system which contains the hetero ring as one of the cyclos
556 ..... Two of the cyclos share at least three ring members or a ring member is shared by three of the cyclos (e.g., bridged, peri-fused, etc.)
557 ..... Tricyclo ring system which contains the hetero ring as one of the cyclos
558 ..... Nitrogen of the hetero ring is shared by an additional cyclo of the tricyclo ring system
559 ..... The additional cyclo has at least six ring members
560 ..... Chalcogen in the tricyclo ring system
561 ..... The additional cyclo consists of one nitrogen and four carbons (e.g., diazepinoindoles, etc.)
562 ..... The additional cyclo consists of two nitrogens and three carbons (e.g., imidazobenzodiazepines, etc.)
563 ..... s-Triazolo(4,3-a)(1,4)-benzodi-azepines (including hydrogenated)
564 ..... Chalcogen, nitrogen, cyano or halogen bonded directly to ring carbon of the triazolo ring
565 ..... Nitrogen attached indirectly to ring carbon of the triazolo ring by acyclic nonionic bonding
566 ..... The unshared ring carbon of the triazolo ring is unsubstituted or alkyl substituted only

567 ..... Bicyclo ring system which contains the hetero ring as one of the cyclos
568 ..... At least three ring hetero atoms in the bicyclo ring system
569 ..... 1,4-benzodiazepines (including hydrogenated)
570 ..... Chalcogen bonded directly to ring carbon of the hetero ring
571 ..... Nitrogen bonded directly to ring carbon of the hetero ring
572 ..... Chalcogen or nitrogen attached indirectly to ring carbon of the hetero ring by acyclic nonionic bonding
573 ..... Chalcogen or nitrogen attached indirectly to ring carbon of the hetero ring by acyclic nonionic bonding
574 ..... Formation of the 1,4-benzodiazepine ring system
575 .... The nitrogens are in the 1,4-positions of the hetero ring
576 ... Polycyclo ring system which contains the hetero ring as one of the cyclos
577 .... Plural nitrogens in the polycyclo ring system
578 ..... Three or more hetero atoms in the polycyclo ring system
579 ..... Nitrogen of the hetero ring is shared by an additional cyclo of the polycyclo ring system
580 ..... The seven-membered hetero ring shares ring members with one other cyclo only
581 .... Two of the cyclos share at least three ring members or a ring carbon is shared by three of the cyclos (e.g., bridged, peri-fused, etc.)
582 ..... Bicyclo ring system which contains the hetero ring as one of the cyclos (e.g., 3-azabicyclo-(3.2.2)nonanes, etc.)
583 ..... Having -C(=X)-, wherein X is chalcogen, bonded directly to ring nitrogen of the bicyclo ring system
584 ..... Chalcogen or nitrogen attached directly to ring nitrogen of the bicyclo ring system by nonionic bonding
585 ..... Chalcogen or nitrogen attached indirectly to ring nitrogen of the bicyclo ring system by acyclic nonionic bonding
586 .... Tricyclo ring system which contains the hetero ring as one of the cyclos
587 ..... The hetero ring shares ring members with each of two benzene rings in the tricyclo ring system (e.g., morphanthridines, etc.)
588 ..... The nitrogen of the hetero ring is bonded directly to each of the two benzene rings (e.g., iminodibenzyl, etc.)
589 ..... Having -C(=X)-, wherein X is chalcogen, bonded directly to ring nitrogen of the tricyclo ring system
590 ..... Nitrogen attached directly or indirectly to ring carbon of the hetero ring by acyclic nonionic bonding
591 ..... Chalcogen attached directly or indirectly to the hetero ring by acyclic nonionic bonding
592 ..... Nitrogen attached indirectly to ring nitrogen of the hetero ring by acyclic nonionic bonding
593 .... Bicyclo ring system which contains the hetero ring as one of the cyclos
594 ..... 3-Benzazepines (including hydrogenated)
595 ..... Benzene ring bonded directly to ring carbon of the hetero ring
596 ... Additional hetero ring attached directly or indirectly to the hetero ring by nonionic bonding
597 .... The additional hetero ring is six-membered and contains nitrogen
598 ..... Plural hetero atoms in the additional hetero ring
599 ..... Polycyclo ring system having the additional hetero ring as one of the cyclos
600 ..... The additional hetero ring is 1,3-diazine (including hydrogenated)
601 ..... The additional hetero ring is 1,3-diazine (including hydrogenated)
602 .... The additional hetero ring is five-membered and contains nitrogen
603 ..... Plural hetero atoms in the additional hetero ring
604 ... Chalcogen attached directly to the hetero ring by nonionic bonding
605 ... Nitrogen attached directly to the hetero ring by nonionic bonding
606 .... Chalcogen, additional nitrogen, or -C(=X)-, wherein X is chalcogen, attached directly to the nitrogen by nonionic bonding
607 ... Having -C(=X)-, wherein X is chalcogen, bonded directly to nitrogen of the hetero ring

608 .... Chalcogen bonded directly to the -C(=X)- group
609 ... Chalcogen or nitrogen attached indirectly to the hetero ring by acyclic nonionic bonding
610 .... The chalcogen or nitrogen is multiple bonded to a carbon (e.g., cyano or carbonyl groups, etc.)
611 ... Benzene ring bonded directly to the hetero ring
612 ... The hetero ring is unsubstituted or alkyl substituted only

FOREIGN ART COLLECTIONS

FOR000 **CLASS-RELATED FOREIGN DOCUMENTS**

This data is current as of August/2002

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L7: Entry 27 of 56 File: USPT Nov 18, 1997

US-PAT-NO: 5688933
DOCUMENT-IDENTIFIER: US 5688933 A

TITLE: Preparation of biologically active compounds from substantially pure enantiomers of 2-azabicyclo[2.2.1]hept-5-en-one

DATE-ISSUED: November 18, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Evans; Christopher Thomas	Heydon			GB2
Roberts; Stanley Micahel	Kenton			GB2

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Chiroscience, Ltd.	Cambridge			GB2	03

APPL-NO: 08/ 461973 [PALM]
DATE FILED: June 5, 1995

PARENT-CASE:
This application is a continuation of application Ser. No. 08/336,754, filed Nov. 8, 1994 U.S. Pat. No. 5,498,625, which is a continuation of Ser. No. 08/035,236 filed Mar. 22, 1993, abandoned, which is a divisional of Ser. No. 07/596,306 filed Oct. 15, 1990 U.S. Pat. No. 5,284,769.

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
GB	8923278	October 16, 1989
GB	8924209	October 27, 1989
GB	9000995	January 17, 1990

INT-CL: [06] C07 H 1/00, C07 D 437/00, C12 P 17/10

US-CL-ISSUED: 536/22.1; 435/121, 435/128, 435/136, 435/147, 435/227, 435/280, 544/265, 548/543
US-CL-CURRENT: 536/22.1; 435/121, 435/128, 435/136, 435/147, 435/227, 435/280, 544/265, 548/543

FIELD-OF-SEARCH: 536/22.1, 435/121, 435/128, 435/136, 435/147, 435/227, 435/280, 544/265, 548/543

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

Search Selected | Search ALL

	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	4421767	December 1983	Palfreyman et al.	514/565
☐	4452991	June 1984	Batchelor et al.	549/383

OTHER PUBLICATIONS

Evans et al., J. Chem. Soc. Perkin Trans., vol. 1:656-657, (1991).
Caamano et al., "An Approach To The Enantioselective Synthesis of 2-Azabicyclo[2.2.1]HEPT-5-EN-3-ONE(1)", Heterocycles, vol. 27, No. 12, pp. 2839-2841, (1988).
Chemical Abstracts, vol. 93, No. 3, Jul. 21, 1980, p. 738, Abstract No. 26738t, Columbus, OH; R.D. Allan et al., "Synthesis of Analogs of GABA. III.. All Four Steroisomers Of 3-Aminocyclopentanecaroxylic Acid And A Stereochemical Correlation With Amidinomycin", Aust. J. Chem., vol. 31(11):2517-2521, (1979).
Chemical Abstracts, vol. 107, No. 5, Aug. 3, 1987, p. 648, Abstract No. 39244k, Columbus, OH; R.D. Allan et al., "Gamma-Aminobutyric Acid Synthesis Of Analogs of GABA. XV.", and Chemical Abstract, vol. 107, Chemicals Substances Index, Part 2, 1987, p. 2891CS, & Australian Journal of Chemistry, 1986, 39(6), 855-864.
Chemical Abstracts, vol. 91, No. 25, Dec. 17, 1979, p. 25, Abstract No. 204205j, Columbus, OH; G.A.R. Johnston et al., "Stereospecific Actions of GABA Analogs", and ADV Pharmacol Ther., Pro. Int. Congr. Phamacol, 7th 1978 (Pub. 1979) 2, 11-18.
Journal of Organic Chemistry, vol. 43, No. 12, Jun. 9, 1978, pp. 2311-2320, American Chemical Society, Washington, D. C., S. Daluge et al., "Synthesis of Carbocyclic Aminucleosides".

ART-UNIT: 188

PRIMARY-EXAMINER: Naff; David M.

ASSISTANT-EXAMINER: Lankford; Blaine

ABSTRACT:

Lactams of 1-amino-3-carboxylic acid cyclic compounds are provided in enantiomeric form, together with an enantiomer of the corresponding ring-opened amino-acid or ester, by reaction of the racemic lactam with a novel lactamase. The products are useful in the synthesis of chiral carbocyclic nucleotides. The enantiomer is preferably 2-azabicyclo[2.2.1]hept-5-en-3-one.

24 Claims, 0 Drawing figures

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L7: Entry 29 of 56 File: USPT Mar 12, 1996

DOCUMENT-IDENTIFIER: US 5498625 A
TITLE: Substantially pure enantieners of 2-azabicyclo(2.2.1)hept-5-en-3-one

Abstract Text (1):
Lactams of 1-amino-3-carboxylic acid cyclic compounds are produced in enantiomeric form, together with an enantiomer of the corresponding ring-opened amino-acid or ester, by reaction of the racemic lactam with a novel lactamase. The products are useful in the synthesis of chiral carbocyclic nucleotides. The enantiomer is preferrably 2-azabicyclo(2.2.1)hept-5-en-3-one. It is desirable to isolate the enantiomer comprising predominantly the (+) enantiomer and a residual amount of the (-) enantiomer, wherein the (+) enantiomer is present in an enantiomeric excess of at least about 88% over the (-) enantiomer or the enantiomer comprising predominantly the (-) enantiomer and a residual amount of the (+) enantiomer, wherein the (-) enantiomer is present in an enantiomeric excess of at least about 98% over the (+) enantiomer.

Brief Summary Text (8):
The present invention is based on the surprising discovery of lactamases that will react with a .gamma.-lactam of formula I to give a single enantiomer of the lactam and the corresponding ring-opened compound of formula II in an enantiomeric form. The enantiomers are novel compounds, and are excellent synthons for a desired enantiomer of Carbovir or a pharmacologically-active analogue.

Brief Summary Text (14):
R.sub.n may be any substituent or substituents which do not interfere with the lactamase reaction; examples of R (if present) are methyl, ethyl, n-butyl, OH, Cl, Br, F, CF.sub.3 and azido. For example, F or another halogen may be a substituent of X, e.g. as --CHHal--. The total number of carbon atoms in the group or groups R will not usually exceed 8. n may be, for example, 1 or 2, but R.sub.n is preferably absent.

Brief Summary Text (16):
It is surprising that material of biological origin will react selectively with a .gamma.-lactam of formula I, to give the desired products in good yield. The material is described herein, for convenience, as a lactamase.

Brief Summary Text (21):
The reaction of the lactam with the material having lactamase activity gives a compound of formula II which can be separated, as necessary or desired, from admixture with the unreacted lactam. If desired, the product (R.sub.2 =H) can be reacted with an acylating agent such as acetic anhydride, to give the corresponding compound (II: R.sub.2 =acyl). Other conventional N-blocking groups can be introduced as desired, examples being CH.sub.2 Ar, COOalk, CONHalk, SO.sub.2 alk, Si(alk).sub.3, CHO and COalk (alk meaning alkyl in its broadest sense).

Brief Summary Text (22):
If the lactamase reaction is conducted in the presence of water, R.sub.1 is H. Alternatively, a nucleophile may be used to introduce an alkyl or other group R.sub.1 directly. For example, the nucleophile is methanol.

Brief Summary Text (24):
One alternative synthesis of the amino-acids (II) is by cleavage of the racemic lactam (I) with a chiral nucleophile (e.g. an amine or alcohol). The cleavage may show some entantioselectivity, and the resultant diastereoisomers can be separated by fractional crystallisation. Acid hydrolysis (if needed) liberates the free amino-acid.

CLAIMS:

1. 2-Azabicyclo(2 2 1)hept-5-en-3-one, comprising predominantly the (+) enantiomer and a residual amount of the (-) enantiomer, wherein the (+) enantiomer is present in an enantiomeric excess of at least about 88% over the (-) enantiomer.

2. The 2-azabicyclo-[2.2.1]hept-5-en-3-one of claim 1,

formed by a process comprising the steps of reacting a racemate of 2-azabicyclo(2.2.1)hept-5-en-3-one with an enzyme having lactamase activity or a microorganism having lactamase activity which stereoselectively cleaves the (-) enantiomer thereby forming the (-) enantiomer of 4-amino-cyclopent-2-ene-1-carboxylic acid or an ester thereof, and then isolating the 2-azabicyclo(2.2.1)hept-5-en-3-one having an enantiomeric excess of the (+) enantiomer.

6. 2-Azabicyclo(2.2.1)hept-5-en-3-one, comprising predominantly the (-) enantiomer and a residual amount of the (+) enantiomer, wherein the (-) enantiomer is present in an enantiomeric excess of at least about 98% over the (+) enantiomer.

7. The 2-azabicyclo-(2.2.1) hept-5-en-3-one of claim 6,

formed by a process comprising the steps of reacting a racemate of 2-azabicyclo(2.2.1)hept-5-en-3-one with an enzyme having lactamase activity or a microorganism having lactamase activity which stereoselectively cleaves the (+) enantiomer thereby forming the (+) enantiomer of 4-aminocyclopent-2-ene-1-carboxylic acid or an ester thereof, and then isolating the 2-azabicyclo(2.2.1)hept-5-en-3-one having an enantiomeric excess of the (-) enantiomer.

11. A composition comprising the (+) enantiomer of 2-azabicyclo(2.2.1)hept-5-en-3-one and the (-) enantiomer of 4-aminocyclopent-2-ene-1-carboxylic acid or an ester thereof-wherein [the]said (+) enantiomer is present in at least about 88% enantiomeric excess over the (-) enantiomer of 2-azabicyclo(2.2.1)hept-5-en-3-one.

12. The composition as claimed in claim 11, which is formed by reacting a .racemate of 2-azabicyclo(2.2.1)hept-5-en-3-one with an enzyme having lactamase activity which stereoselectively cleaves the (-) enantiomer, thereby forming the (-) enantiomer of 4-aminocyclopent-2-ene-1-carboxylic acid or an ester thereof.

13. The composition as claimed in claim 11, which is formed by reacting a racemate of 2-azabicyclo(2.2.1)hept-5-en-3-one with a microorganism having lactamase activity which stereoselectively cleaves the (-) enantiomer, thereby forming the (-) enantiomer of 4-aminocyclopent-2-ene-1-carboxylic acid or an ester thereof.

15. A composition comprising the (-) enantiomer of 2-azabicyclo(2.2.1)hept-5-en-3-one and the (+) enantiomer of 4-aminocyclopent-2-ene-1-carboxylic acid or an ester thereof, wherein said (-) enantiomer is present in at least about 98% enantiomeric excess over the (+) enantiomer of 2-azabicyclo(2.2.1)hept-5-en-3-one.

16. The composition as claimed in claim 15, which is formed by reacting a racemate of 2-azabicyclo(2.2.1)hept-5-en-3-one with an enzyme having lactamase activity which stereoselectively cleaves the (+) enantiomer, thereby forming the (+) enantiomer of 4-aminocyclopent-2-ene-1-carboxylic acid or an ester thereof.

17. The composition as claimed in claim 15, which is formed by reacting a racemate of 2-azabicyclo(2.2.1)hept-5-en-3-one with a microorganism having lactamase activity which stereoselectively cleaves the (+) enantiomer, thereby forming the (+) enantiomer of 4-aminocyclopent-2-ene-1-carboxylic acid or an ester thereof.

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L7: Entry 1 of 56 File: USPT Jul 23, 2002

US-PAT-NO: 6423522
DOCUMENT-IDENTIFIER: US 6423522 B1

TITLE: Microorganism lactamase enzyme obtained therefrom and their use

DATE-ISSUED: July 23, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Wisdom; Richard Anthony	Cambridge			GB
Lee; Caroline Susan	Cambridgeshire			GB
Brown; Robert Christopher	Cambridge			GB

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Chirotech Technology, Ltd.				GB	03

APPL-NO: 09/ 510949 [PALM]
DATE FILED: February 22, 2000

PARENT-CASE:
CROSS-REFERNCE TO RELATED APPLICATION This application is a division of application Ser. No. 08/922,865, filed Sep. 3,1997 now U.S. Pat. No. 6,090,616.

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
GB	9618340	September 3, 1996

INT-CL: [07] C12 N 9/14

US-CL-ISSUED: 435/195; 435/174, 435/176, 435/177, 435/231, 435/227
US-CL-CURRENT: 435/195; 435/174, 435/176, 435/177, 435/227, 435/231

FIELD-OF-SEARCH: 435/174, 435/176, 435/177, 435/195, 435/231, 435/227

PRIOR-ART-DISCLOSED:

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
0424064	April 1991	EP	

OTHER PUBLICATIONS

Taylor, S.J.C., R. McCague, R. Wisdom, C. Lee, K. Dickson, G. Ruecroft, F. O'Brien, J. Littlechild, J. Beven, S. Roberts, C. Evans (1993) "Development of the Biocatalytic Resolution of 2-azabicyclo[2.2.1]hept-5-en-3-one as an entry to Single-Enantiomer Carbocyclic Nucleosides" Tetrahedron Asymmetry 4(6):1117-1128.
Brabban, A.D., J. Littlechild, R. Wisdom (1996) Stereospecific .gamma.-lactamase activity in a Pseudomonas fluorescens species Journal of Industrial Microbiology 16:8-14.

Comamonas acidovorans, NCIMB 40827.

6423522 . 22 Feb 00; 23 Jul 02. Microorganism lactamase enzyme obtained therefrom and their use. Wisdom; Richard Anthony, et al. 435/195; 435/174 435/176 435/177 435/227 435/231. C12N009/14.

Comamonas acidovorans, NCIMB 40827.

Krieg, N.R. (1984) "Bergey's manual of systematic bacteriology" see p. 78, right-hand column and pp. 179-180, abstract No. XP002048230.

ART-UNIT: 1651

PRIMARY-EXAMINER: Prats; Francisco

ABSTRACT:

A lactamase enzyme having good stability, capable of hydrolysing an enantiomer of the bicyclic lactam, 2-azabicyclo[2.2.1]hept-5-en-3-one, to give (-) lactam and (+) amino acid, has been found in a strain of Comamonas acidivorans. The enzyme has been isolated and cloned, and its structure identified.

8 Claims, 0 Drawing figures
Exemplary Claim Number: 1

BRIEF SUMMARY:

1 FIELD OF THE INVENTION

2 This invention relates to a microorganisms lactamase enzyme obtained therefrom, and their use.

3 BACKGROUND OF THE INVENTION

4 The bicyclic .gamma.-lactam, 2-azabicyclo 2.2.1hept-5-en-3-one, is a useful synthon hat can be used for the production of carbocyclic nucleosides which are gaining in importance as therapeutic agents. Published areas to which such nucleosides are being targeted include antivirals (e.g. Vince and Hua. J. Med. Chain., 33:17-21 (1990), againts e.g. HIV) and cardiac vasodilators (adenosine agonists). A major benefit of the carbocyclyc in such agents is its resistance to breakdown by enzymes in the body. By comparison, naturally-occurring ribosyl nucleosides may be more readily cleaved by nucleases, so that their bioactivity is lost.

5 Although carbocyclic nucleosides are known in nature e.g. Aristeromycin from Streptomyces citricolor, natural yields tend to be low and the isolated products have then to be further manipulated to obtain more useful compounds. A more econonic route is to synthesise the required compounds chemically, sarting from the .gamma.-lactam. However, as chemically synthesised, .gamma.-lactam is racemic By conventional synthesis, the ultimate drug will also be a mixture of enantiomers, which causes regulatory concerns if one of the enantiomers is not very active or causes unwanted side-efects. There is a need therefore to put a step into the synthesis where either of the two enantiomers of a racemic synthon can be isolated and the rest of the drug then built on it.

6 An effective way of doing this is to use an enzyme to selectively hydrolyse one enantiomer of the racemic .gamma.-lactam across the amide bond, to give the cyclic amino acid compound and leave the other enantiomer. The remaining lactam can then be readily separated from the amino acid product by extraction into dichloromethane, purfied by crystailltisation and used in subsequent downstream chemistry to build up the required drug. By careful selection of the right enzyme it is possible to find an enzyme highly selectively for only one of the lactam enantiomers such that at marginally greater than 50% conversion, lactam of high ee (>90%) remains. Enzymes have been found that are selective for either of the two enantiomers.

7 EP-A-0424064 discloses methods for carrying out the above described resolution and provides two organisms that produce enzymes that have the different selectivities. A Rhodococcus strain produces an enzyme which hydrolyses the (-) lactam, enabling the (+) lactam to be isolated for further use. whereas a Pseudomonad produces an emzyme which hydrolyses the (+) lactam, enabling

isolation of the (-) lactam.

8 Further enzymes that carry out these selective hydrolyses have also been described in the literature. Thus Taylor et al, Tetrahedron: Asymmetry, 4 (6):1117-1128 (1993), describe an enzyme selective for hydrolysis of the (+) lactam from a strain of Pseudonomas fluorescens and an enzyme selective for the (-) lactam from a strain of Aureobacterium. A further enzyme selective for the hydrolysis of the (+) lactam has been described by Brabban et al. J. Ind. Microbiology. 16:8-14 (1996).

9 In order to develop a robust industrial biotransformation process, it is desirable to use an enzyme or whole cell biocatalyst that is relatively stable. This can enable biocatalyst recycling and re-use through immobilisation, thus greatly reducing biocatalyst cost and enabling handling of the biocatalyst on a large scale without significant losses of activity. It is also often found that more stable biocatalysts are better able to tolerate high substrate and/or product concentrations without inactivation. This then enables biotransformation to be run at the highest concentration of reactants possible, given kinetic and handling constraints. This has two advantages: it results in minimal reactor volume requirements and also minimises liquid handing volumes during product work-up.

10 Taylor et al, supra. describe a lactamase from Aireobacterium especies that is very stable at elevated temperatures and which selectively hydrolyses the (-) .gamma.-lactam, giving the (+) .gamma.-lactam and (-) amino acid as a product. The enzyme from this organism has been immobilised and maintains its stability over months of operation. No enzyme with good stability and the opposite selectivity is known, although Brabban at al, Supra, screened a number of different potential isolates. Previous work with Pseudomonad type organisms displaying the required lactamase activity had shown them to have poor stability. This is unfortunate since it is the (-) .gamma.-lactam which is the more usefwl synthon, having the more natural stereochemistry and making it easier to build up functionality than for instance the (-) amino acid formed by the action of the Aireobacterium lactamase. There is therefore a need for a stable .gamma.-lactamase with high selectivity for the hydrolysis of the (+) bicyclic .gamma.-lactam.

11 SUMMARY OF THE INVENTION

12 Surprisingly, it has been found that a strain of Comamonas acidivorans, which was isolated from the environment, produces an enzyme of high potential for use in an industrial process for resolution of the required .gamma.-lactam. This enzyme is not only much more temperature-stable than previously identified (+) .gamma.-lactamase, but it also enables the bioresolution to be carried out at very high substrate/product concentrations. This organism has been deposited at the NCIMB, 23 St. Machar Street, Aberdeen, UK, on 30th August 1996, under the terms of the Budapest Treaty, where it has been given the accession number NCIMB 40827.

13 The gene encoding the .gamma.-lactamase has been isolated and sequenced (see SEQ ID NO:1), and the enzyme's amino-acid sequence derived (see SEQ ID NO:2). This invention relates to compounds having this structure, and fragments thereof having the same activity, as will be readily evident to one of ordinary skill in the art. The novel enzyme is characterised by its stability, i.e. one or more of the following: greater than 85% retention of activity after being held at 40.degree. C. for 4 hours or greater than 30% activity after being held at 60.degree. C. for 4 hours; hydrolysis at an initial concentration of 100 g racemic lactam plus 300 ml buffer and continuing to at least 90% hydrolysis of the (+) lactam with less than 5% hydrolysis of the (-) lactam.

DETAILED DESCRIPTION:

1 DESCRIPTION OF THE INVENTION

2 The novel enzyme is useful for the enantiospecific hydrolysis of a mixture of enantiomers of the required .gamma.-lactam, e.g. a racemic mixture. After reaction, the residual (-) lactam may readily be separated from the (+) amino-acid formed by hydrolysis. Both these reactions may be conducted under conditions known to those of ordinary skill in the art.

3 The enzyme may be used in whole cell or isolated form. It may be immobilised, if desired, by methods known to those of ordinary skill in the art.

4 The enzyme may be produced from the deposited organism. Alternatively, it may be produced by recombinant technology.

5 Using the DNA and amino-acid sequence provided herein, a person skilled in the art can readily construct fragments or mutations of the genes and enzymes disclosed herein. These fragments and mutations, which retain the activity of the exemplified enzyme, are within the scope of the present invention. Also, because of the redundancy of the genetic code, a variety of different DNA sequences can encode the amino-acid sequences disclosed herein. It is well within the skill of one of ordinary skill in the art to create these alternative DNA sequences encoding the same, or similar, enzymes. These DNA sequences are within the scope of the present invention. As used herein, reference to "essentially the same" sequence refers to sequences which have amino-acid substitutions, deletions, additions or insertions which do not materially affect activity. Fragments retaining activity are also included in this definition.

6 The genes of this invention can be isolated by known procedures and can be introduced into a wide variety of microbial hosts. Expression of the gene results, directly or indirectly, in the intracellular production and maintenance of the enzyme. The gene may be introduced via a suitable vector into a microbial host.

7 A wide variety of ways are available for introducing the gene into the microorganism host under conditions which allow for stable maintenance and expression of the gene. A DNA construct may include the transcriptional and translational regulatory signals for expression of the gene, the gene under their regulatory control and a DNA sequence homologous with a sequence in the host organism, whereby integration will occur, and/or a replication system which is functional in the host, whereby integration or stable maintenance will occur.

8 In the direction of transcription, namely in the 5' to 3' direction of the coding or sense sequence, the construct can involve the transcriptional regulatory region, if any, and the promoter, where the regulatory region may be either 5' or 3' of the promoter, the ribosomal binding site, the initiation codon, the structural gene having an open reading frame in phase with the initiation codon, the stop codon(s), the polyadenylation signal sequence, if any, and the terminator region. This sequence as a double strand may be used by itself for transformation of a microorganism host, but will usually be included with a DNA sequence involving a marker.

9 The gene can be introduced between the transcriptional/translational initiation and termination regions, so as to be under the regulatory control of the initiation region. This construct can be included in a plasmid, which could include at least one replication system, but may include more than one, where one replication system is employed for cloning during the development of the plasmid and the second replication system is necessary for functioning in the ultimate host. In addition, one or more markers may be present, as described above. Where integration is desired, the plasmid will desirably include a sequence homologous with the host genome.

10 The transformants can be isolated in accordance with conventional ways, usually employing a selection technique, which allows for selection of the desired organism as against unmodified organisms or transferring organisms, when

present. The transformants then can be tested for activity.

11 Suitable host cells include prokaryotes and eukarotes. An example is E. coli.

12 The following Examples illustrate the invention.

13 1. Isolation of Potential .gamma.-Lactamase Producing Straints

14 Approximately 1 g of soil from a ditch was mixed with 20 ml 50 mM potassium phosphate buffer, pH7, mixed well and shaken at room temperature for 30 minutes. A 0.4% inoculum of this suspension was then placed into 25 ml enrichment medium in a conical flask and shaken at 30.degree. C. for 41 hours. The following enrichment medium was used:

	(g .multidot. l.sup.-1)
Yeast extract	0.1
NH.sub.4 Cl	2.0
KH.sub.2 PO.sub.4	7.0
Na.sub.2 HPO.sub.4	2.0
MgSO.sub.4	0.4
CaCl.sub.2	0.2
Trace element solution	0.2
Racemic bicyclic .gamma.-lactam	2.0
5M NaOH	to pH 7

15 the trace element solution comprised:

	(g .multidot. l.sup.-1)
CaCl.sub.2.2H.sub.2 O	3.6
ZnO	2.0
CuCl.2H.sub.2 O	0.85
Na.sub.2 MoO.2H.sub.2 O	4.8
MnCl.sub.2.4H.sub.2 O	2.0
FeCl.sub.3.6H.sub.2 O	5.4
H.sub.3 BO.sub.3	0.3
CoCl.sub.2.6H.sub.2 O	2.4
Conc HCl	250 ml

16 A 0.5% inoculum was then transfered into a second enrichment flask (25 ml) of the same medium, and grown for a further 94 hours. At this point, samples were taken from the flask, diluted in 10 mM phosphate buffer, pH 7.0 and plated onto the following medium:

	(g .multidot. l.sup.-1)
Yeast extract	0.1
NH.sub.4 Cl	2.0
KH.sub.2 PO.sub.4	7.0
Na.sub.2 HPO.sub.4	2.0
MgSO.sub.4	0.4
CaCl.sub.2	0.2
Trace element solution	0.2
Noble Agar	15.0
5M NaOH	to pH 7

17 2.0 g.l.sup.-1 N-acetyl-L-phenylanaline was then filter sterilised into the above autoclave medium on cooling, prior to pouring the plates. After 6 days incubation at 30.degree. C., colonies were picked, and purified on further agar plates and then used in the screening study.

18 2. Screening of Recovered Isolates

19 Isolated colonies were grown in the following medium:

	(g .multidot. l.sup.-1)
Yeast extract	5.0
NH.sub.4 Cl	2.0
KH.sub.2 PO.sub.4	7.0
Na.sub.2 HPO.sub.4	2.0
MgSO.sub.4	0.4
CaCl.sub.2	0.2
Trace element solution	1.0
Racemic bicyclic .gamma.-lactam	2.0
Glucose	10.0
5M NaOH	to pH 7

20 A colony was inoculated into 4 ml filter-sterilised medium in a sterile plastic container and grown for about 24 hours in a shaker at 30.degree. C.

21 Cultures were then centrifuged and the pellet resuspended in 1 ml 50 mM phosphate buffer, pH7. To this was then added 1 ml 100 g.l.sup.-1 racemic bicyclic .gamma.-lactam in a similar buffer. Reactions were carried out at 30.degree. C. with shaking. Samples were taken over the next 7 days and assayed for conversion of the lactam by HPLC. For those reactions showing significant hydrolysis, enantiomeric excess (ee) was determined by GC.

22 One strain which was isolated showed desirable characteristics. In the initial screen this strain achieved 52% conversion of the added substrate after 144 hours biotransformation, and the residual lactam was shown to be the (-) enantiomer with an ee of >99%. Identification by the NCIMB showed the organism to be a strain of Comamonas acidovorans. This strain has been deposited at the NCIMB, as described above.

23 The following analytical methods were employed:

24 Extent of Hydrolysis (HPLC). Samples were diluted as appropriate and 20 .mu.l injected onto a 15 cm Kromasil C-8 column. The elution buffer was 50% methanol in 10 mM phosphate buffer, pH 7;. flow rate 1 ml.min.sup.-1 ; run time 5 minutes. Detection was at .lambda.=225 nm.

25 ee of reaction products (GC). Samples were extracted into ethyl acetate, dried with anhydrous magnesium sulphate and injected onto a 50 m CP Cyclodextrin capillary column. The oven temperature was increased from an initial 140 to 200.degree. C. during the analysis.

26 3. Fermentation

27 Seed flasks were prepared using the following medium:

	(g .multidot. l.sup.-1)
Yeast extract	10
(NH.sub.4).sub.2 SO.sub.4	1
KH.sub.2 PO.sub.4	5
MgSO.sub.4.7H.sub.2 O	0.1
CaCl.sub.2.2H.sub.2 O	0.05
Trace elements	0.1
NaOH	to pH 7

28 The trace element solution is as defined above, except that the amount of conc. HCl is 333 ml.l.sup.-1.

29 75 ml medium was prepared in a 500 ml conical flask. Flasks were inoculated with the organism, and incubated with shaking at 25.degree. C. till an absorbance (520 nm) of between 3.5 and 7 had been achieved. Cells were then inoculated at 0.1% into the fermenter having 1.5 L of the following (sterilised) medium:

	(g .multidot. l.sup.-1)
Yeast extract	20
(NH.sub.4).sub.2 SO.sub.4	2
KH.sub.2 PO.sub.4	5
MgSO.sub.4.7H.sub.2	0.5
CaCl.sub.2.2H.sub.2 O	0.1
Trace elements	1.0
Succinic acid	10
PPG 2025	2 ml
NaOH	to pH 7

30 Initial temperature was 25.degree. C. and the pH was controlled at 7.1. A constant air flow rate of about 0.5 vvm was maintained, with the agitation being varied between 500 and 1000 rpm to maintain aerobic conditions. After 18.6 hours, a slow feed of concentrated yeast extract was initiated at a rate equivalent to 2 g yeast extract added per initial litre per hour, i.e. 3 g per hour. The fermentation was completed 24 hours later, the cells harvested by centrifugation and stored as a cell paste in the freezer for further use. A total biomass of about 82 g wet cells was collected and the final fermentation activity yield was 0.45 U.ml.sup.-1 (where 1 U is 1 .mu.mole .gamma.-lactam hydrolysed per minute).

31 4. Temperature Stability

32 35.8 g of cell paste was thawed and added to 700 ml lysis buffer, containing 10 mM sodium phosphate (pH 7), 10 mM EDTA, 0.1% Triton X-100, 5 mM dithiothreitol and 1 mg.ml.sup.-1 lysozyme. The lysis buffer was stirred at room temperature for 5.5 hours, then 37 ml of a 5% solution of polyethylenimine, adjusted to pH 7 with HCl, was added and stirred for a further hour before recovering the supernatant by centrifugation.

33 To 500 ml supernatant was slowly added 174 g ammonium sulphate with good mixing to dissolve the salt. After 20 minutes, the precipitate was harvested by centrifugation and resuspended with 100 ml 10 mM sodium phosphate, pH 7. This was then dialysed against 2 times 5 L 10 mM sodium phosphate, pH 7.1, and then stored in the freezer.

34 For the temperature stability tests, the frozen dialysate was thawed and 2.times.2.5 ml samples buffer exchanged into 3.5 ml phosphate-buffered saline (PBS) or 10 mM Tris buffer, pH 8.0 using mini Sephadex G-25 gel filtration columns. Buffer exchange into the 10 mM Tris buffer resulted in a precipitate (which contained some activity) which was removed by centrifugation. Samples of each preparation were then placed in a 60.degree. C. hot block, a 40.degree. C. water bath or a 25.degree. C. incubator. Samples were taken at 1, 2 and 4.3 hours and analysed for residual lactamase activity. The following results were obtained after 4.3 hours incubation:

Temperature	Residual Activity

Buffer	(.degree. C.)	(% of start)
PBS	25	97
PBS	40	87
PBS	60	32
Tris (pH 8)	25	110
Tris (pH 8)	40	105
Tris (pH 8)	60	45

35 By comparison, the Pseudomonas fluorescens .gamma.-lactamase described by Brabban et al, supra, lost up to 70-80% of its activity over 4 hours at 37.degree. C. The novel enzyme is clearly much more temperature-stable. This opens up the possibility of immobilising the enzyme onto a solid support and re-using it in many biotransformations, thereby greatly reducing its cost impact on the process.

36 5. Whole-cell Biotransformation

37 Frozen cell paste (25 g), obtained in a similar fermentation to that described in Example 3, excepting that the final enzyme yield in this case was measured to 0.67 U.ml.sup.-1, was thawed and stirred in 50 mM KH.sub.2 PO.sub.4 (300 ml, pH7). .gamma.-Lactam (100 g) was added as solid to this, then the reaction stirred at 25.degree. C: for 24 hours. Celite (28 g) then polyethylenimine (28 ml of 5% solution in water) were added, followed by isopropanol (175 ml). After stirring for a further 10 minutes, the solids were removed by filtration, then the filtrate evaporated in vacuo to 200 ml volume. The aqueous was extracted 5 times with dichloromethane (200 ml), then the organic extracts dried using anhydrous MgSO.sub.4. The filter-cake was washed with acetone (150 ml) and the extract dried (with anhydrous MgSO.sub.4), then all the combined organic fractions evaporated in vacuo to dryness. This yielded 44.3 g of an off-white solid, which was analysed to be (-) lactam having an ee of >99%.

38 This biotransformation could be carried out at a very high substrate concentration (1 g substrate per 3 ml buffer) and could still provide complete hydrolysis of the (+) lactam enantiomer. This is therefore highly volume-efficient, which enables the (-) lactam to be produced in a minimal volume, thus reducing liquid handling requirements and reducing batch biotransformation reactor volume requirements.

39 6. Identification and Isolation of the Gene

40 A quantity of cell paste (500 mg) was treated by the addition of TESS buffer (50 mM Tris.HCl [pH 8.0], 10 mM EDTA, 25 mM NaCl, 25% w/v Sucrose) supplemented with lysozyme (1.5 mg ml.sup.-1). This treatment was carried out at 37.degree. C. for 1 hr and the resulting sphereoplasts were lysed by the addition of 10% SDS (1.5% final conc.) To the cell lysate, solid caesium chloride was added at 1 g ml.sup.-1. Once dissolved, ethidium bromide was added at 80 .mu.g ml.sup.-1 final conc. The suspension was then loaded into Sorvall Ultracrimp ultracentrifuge tubes and a gradient was established by centrifugation at 30,000 rpm at 20.degree. C. for 72 hrs. Once resolved and visualised by an intense ethidium bromide band, the genomic DNA was removed by syringe. Ethidium bromide was removed by extraction with caesium chloride-saturated butanol. Finally, the genomic DNA was dialysed in 10,000 volumes of TE buffer (10 mM Tris.HCl, 1 mM EDTA [pH 8.0]) with two changes.

41 A genomic library was prepared by a time-course partial restriction digest with Sami3A I (Promega Corp.) restriction endonuclease. Horizontal agarose gel

electrophoresis resolved DNA fragments in the range of 1.0-4.0 kb. These fragments were excised by electroelution in TBE (16mM Tris. HCl [pH 8.0], 8mM Boric acid, 400 .mu.M EDTA) at 25 mA current. The eluted DNA fragments were purified by extraction with an equal volume of Tris-buffered phenol:chloroform and ethanol precipitation. The Sati3A I partial genomic DNA fragments were ligated into pUC19; see Yanish-Peron et al, Gene 33:103-119 (1985). The cloning vector pUC19 had been previously linearised by BamHI (Promega Corp.) restriction digestion and 5'-phosphate groups were removed by Calf Intestinal Alkaline Phosphatase (Promega Corp.) to prevent re-ligation. Ligations were carried out at 14.degree. C. with various ratios of vector and genomic fragments using T4 DNA ligase (Boehringer Mannheim Ltd). Ligation reactions were transformed into Max Efficiency E. coli DH5.alpha. (Gibco BRL Life Sciences), transformed E. coli were plated onto Tryptone Soya Agar (Oxoid Ltd) supplemented with ampicillin (100 .mu.g ml.sup.-1), X-Gal (50 .mu.g ml.sup.-1), and 1 rnM IPTG. After overnight incubation at 37.degree. C., transformed E. coli colonies were adsorbed onto Whatman 2 filter paper discs impregnated with 20mg ml.sup.-1 (+)-lactam in methanol. Filters were incubated at room temperature for 4 hrs and developed with 2% w/v ninhydrin in acetone. After developing at 60.degree. C., a distinctive brown halo upon a purple background, indicative of amino acid production, could be clearly seen around a single colony. The single lactamase-expressing clone was isolated and lactamase activity was verified by Achiral and Chiral HPLC assay.

42 7. Characterisation and Sequencing of Lactamase Gene

43 Plasmid DNA was prepared from the lactamase-expressing clone. Restriction digest analysis showed the presence of a 1.9 kb Sau3A I restriction fragment. DNA sequence analysis of the inserted fragment showed this fragment to incorporate a open reading frame (ORF) of 1.6 kb which, when driven by the upstream lac promoter of pUC19, translates to a protein of 575 residues (61 kDa.); see the Sequence Listing. The deduced amino acid sequence of the translated ORF shows >65% homology to the acetamidase from Mycobacterium smegmatis and Methylophilus methylotrophus. These enzymes have been shown to hydrolyse short chain fatty acylamides; see Draper, J. Gen. Microbiol. 46:111-123 (1969).

44 With reference to the Sequence Listing, the 1.9 kb lactamase fragment resides within the two preserved BamHI restriction sites. Sequence 5' to the insert incorporates the lac promoter and ribosome-binding site of pUC 19.

45 The pUC 19 construct carrying the lactamase gene was subsequently modified by the insertion of the cer element from the wild-type E. coli plasmid ColE 1. This construct was designated pPET1.

46 As will be understood, E. coli plasmid pPET1 was derived from pUC19, which harbours a 1.9 kb Sau3A I genomic fragment from Comomonas acidovorans ligated into the BamHI restriction site. The cer stability element of the wild type plasmid ColE 1 was inserted 3' to the lactamase fragment via BamHI (partial) and NdeI restriction.

47 8. Growth of Recombinant Lactamase

48 Recombinant E. coli strain was inoculated into a 1 litre baffled shake flask containing 100 ml TSB medium (Oxoid Ltd.) supplemented with ampicillin (100 gg ml.sup.-1). The flask and inoculum were incubated for 16 hr at 37.degree. C., shaking at 300 rpm in orbital shaker (25mm throw). The seed culture was inoculated (1%) into a 2.8 litre laboratory bioreactor vessel containing 1.5 litres TSB medium. The temperature was maintained at 25.degree. C. pH 7.0, and dissolved O.sub.2 tension at >50%. Growth was monitored at 520.sub.nm, optical density against a TSB medium blank. After 24 hr growth, cells were harvested by centrifugation (5000 g at 4.degree. C. for 10 min.). Cells were stored at -20.degree. C. until required.

49 9. Use of Recombinant Cells

The E. coli strain harbouring the recombinant plasmid pPET1, was grown and stored as described above. Cells were resuspended at 10% w/v in 100 mM Tris.HCl, pH 7.5. Racemic lactam was resuspended of 100mg.mll in 100 mM Tris.HCl, pH 7.5. Reaction conditions for the biotransformation of (+)-lactam were 10mg ml.sup.-1 of racemic lactam mixed with 0.1% w/v recombinant cells in 100 mM Tris.HCl, pH 7.5. The suspension was reacted at 25.degree. C., shaking at 225 rpm for 1 hr. HPLC analysis after 1 hr reaction showed the conversion of 30% of (+)-lactam to acid with a selectivity of >95% ee.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(iii) NUMBER OF SEQUENCES: 2

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1951 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Comamonas acidovorans

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 49..1773

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1

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CGCTCGTATG TTGGGATGTG AGCGATACAA TTTCACACAG GAACAGCT ATG ACC ATG      57
                                                     Met Thr Met
                                                       1

ATA ACG CCA AGC TTG CAT GCC TCG GCA GGT CGG ACT CTA GAG GAT CCG      105
Ile Thr Pro Ser Leu His Ala Ser Ala Gly Arg Thr Leu Glu Asp Pro
  5                  10                  15

TTT TTT CCC ACT GCC ATC GCA AGG AGC ACA CCA TGG CCG GAA ACC CTG      153
Phe Phe Pro Thr Ala Ile Ala Arg Ser Thr Pro Trp Pro Glu Thr Leu
 20                  25                  30                  35
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ATC AAG GTC GAT CTC AAC CAG TCC CCC TAC GAC AAC CCG CAG GTG CAC      201
Ile Lys Val Asp Leu Asn Gln Ser Pro Tyr Asp Asn Pro Gln Val His
                40                  45                  50
AAC CGC TGG CAT CCC GAC ATT CCC ATG GCG GTC TGG GTG GAG CCG GGC      249
Asn Arg Trp His Pro Asp Ile Pro Met Ala Val Trp Val Glu Pro Gly
            55                  60                  65
GCG GAG TTC AAG CTG GAG ACC TAT GAC TGG ACC GGC GGC GCC ATC AAG      297
Ala Glu Phe Lys Leu Glu Thr Tyr Asp Trp Thr Gly Gly Ala Ile Lys
        70                  75                  80
AAC GAC GAC AGC GCC GAA GAC GTG CGC GAC GTG GAT CTG TCC ACC GTC      345
Asn Asp Asp Ser Ala Glu Asp Val Arg Asp Val Asp Leu Ser Thr Val
    85                  90                  95
CAC TTC CTG TCC GGC CCC GTG GGC GTG AAG GGC GCG CAG CCC GGC GAC      393
His Phe Leu Ser Gly Pro Val Gly Val Lys Gly Ala Gln Pro Gly Asp
100                 105                 110                 115
CTG CTG GTG GTG GAC CTG CTG GAC ATC GGC GCG CGC GAC GAC AGC CTC      441
Leu Leu Val Val Asp Leu Leu Asp Ile Gly Ala Arg Asp Asp Ser Leu
                120                 125                 130
TGG GGC TTC AAC GGC TTT TTC TCC AAG CAG AAT GGC GGC GGC TTC CTG      489
Trp Gly Phe Asn Gly Phe Phe Ser Lys Gln Asn Gly Gly Gly Phe Leu
            135                 140                 145
GAC GAG CAT TTC CCG CTG GCC CAG AAG TCC ATC TGG GAC TTC CAC GGC      537
Asp Glu His Phe Pro Leu Ala Gln Lys Ser Ile Trp Asp Phe His Gly
        150                 155                 160
ATG TTC ACC AAG AGC CGC CAC ATC CCC GGC GTC AAC TTC GCA GGC CTC      585
Met Phe Thr Lys Ser Arg His Ile Pro Gly Val Asn Phe Ala Gly Leu
    165                 170                 175
ATC CAC CCG GGC CTG ATC GGC TGC CTG CCC GAC CCC AAG ATG CTG GCC      633
Ile His Pro Gly Leu Ile Gly Cys Leu Pro Asp Pro Lys Met Leu Ala
180                 185                 190                 195
AGC TGG AAT GAG CGC GAG ACC GGC CTC ATC GCC ACC GAC CCC GAC CGC      681
Ser Trp Asn Glu Arg Glu Thr Gly Leu Ile Ala Thr Asp Pro Asp Arg
                200                 205                 210
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ATT CCC GGC CTG GCC AAC CCG CCC AAC GCC ACC ACC GCC CAC ATG GGC      729
Ile Pro Gly Leu Ala Asn Pro Pro Asn Ala Thr Thr Ala His Met Gly
            215                 220                 225
CAG ATG CAG GGC GAG GCG CGC GAC AAG GCC GCC GCC GAA GGC GCA CGC      777
Gln Met Gln Gly Glu Ala Arg Asp Lys Ala Ala Ala Glu Gly Ala Arg
        230                 235                 240
ACC GTG CCG CCG CGC GAG CAC GGC GGC AAC TGC GAC ATC AAG GAC CTC      825
Thr Val Pro Pro Arg Glu His Gly Gly Asn Cys Asp Ile Lys Asp Leu
    245                 250                 255
TCG CGC GGC TCG CGC GTG TTC TTC CCC GTC TAC GTG GAC GGC GCG GGC      873
Ser Arg Gly Ser Arg Val Phe Phe Pro Val Tyr Val Asp Gly Ala Gly
260                 265                 270                 275
CTG AGC GTG GGC GAC CTG CAC TTC AGC CAG GGT GAT GGC GAG ATC ACC      921
Leu Ser Val Gly Asp Leu His Phe Ser Gln Gly Asp Gly Glu Ile Thr
                280                 285                 290
TTC TGG GGG CCC ATC GAG ATG CCC GGC TGG GTG CAC ATG AAG GTC TCG      969
Phe Trp Gly Pro Ile Glu Met Pro Gly Trp Val His Met Lys Val Ser
            295                 300                 305
CTG ATC AAG GGC GGC ATG GCC AAG TAC GGC ATC AAG AAC CCC ATC TTC     1017
Leu Ile Lys Gly Gly Met Ala Lys Tyr Gly Ile Lys Asn Pro Ile Phe
        310                 315                 320
AAG CCC AGC CCC ATG ACG CCC AAC TAC CAA GGA CTA CCT GAT CTT CGA     1065
Lys Pro Ser Pro Met Thr Pro Asn Tyr Gln Gly Leu Pro Asp Leu Arg
    325                 330                 335
AGG CAT CTC GGT GGA CGA AAA GGG CAA GCA GCA CTA CCT GGA CGT GAC     1113
Arg His Leu Gly Gly Arg Lys Gly Gln Ala Ala Leu Pro Gly Arg Asp
340                 345                 350                 355
CGT GGC CTA CCG CCA GGC CTG CCT GAA CGC CAT CGA GTA CCT GAA GAA     1161
Arg Gly Leu Pro Pro Gly Leu Pro Glu Arg His Arg Val Pro Glu Glu
                360                 365                 370
ATT CGG CTA CAG CGG CGC CCA GGC CTA CTC GCT GCT GGG CAC GGC GCC     1209
Ile Arg Leu Gln Arg Arg Pro Gly Leu Leu Ala Ala Gly His Gly Ala
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            375                 380                 385
CGT GCA GGG CCA CAT CAG CGG CGT GGT GGA CGT GCC CAA TGC CTG CGC     1257
Arg Ala Gly Pro His Gln Arg Arg Gly Gly Arg Ala Gln Cys Leu Arg
        390                 395                 400
CAC GCT GTG GCT GCC CAC GGA GAT CTT CGA CTT CGA CAT CAA TCC CAC     1305
His Ala Val Ala Ala His Gly Asp Leu Arg Leu Arg His Gln Ser His
    405                 410                 415
GGC CGA GGG ACC ACA GAA GAT CAT CAC GGG CGG GGT GGA TCT GCC CAT     1353
Gly Arg Gly Thr Thr Glu Asp His His Gly Arg Gly Gly Ser Ala His
420                 425                 430                 435
CGC CCA GGA CAA GTA AGC CCG GCA TAC GAC ACC CGC CAT CCA CCA TTC     1401
Arg Pro Gly Gln Val Ser Pro Ala Tyr Asp Thr Arg His Pro Pro Phe
                440                 445                 450
GCC AGA GGC CGC CCA TGC CCA CCT ATG ACT ACC ACT GCA CCG CAT GCG     1449
Ala Arg Gly Arg Pro Cys Pro Pro Met Thr Thr Thr Ala Pro His Ala
            455                 460                 465
GCG GCT TCG ACG CGC TGC GCA GCC TCT CGC AGC GCA ACG AGC CCG CGC     1497
Ala Ala Ser Thr Arg Cys Ala Ala Ser Arg Ser Ala Thr Ser Pro Arg
        470                 475                 480
CCT GCC CCA GCT GCG AGG CGG CCT CGC CCC GCG TCT TCG TCA GCG CGC     1545
Pro Ala Pro Ala Ala Arg Arg Pro Arg Pro Ala Ser Ser Ser Ala Arg
    485                 490                 495
CGC GCC TGG CCT GCA CCA GCC CCG AAC AGC GCC GCG CCC ACG ACA CCA     1593
Arg Ala Trp Pro Ala Pro Ala Pro Asn Ser Ala Ala Pro Thr Thr Pro
500                 505                 510                 515
ACG AGC GCG CCC GGC ACG AGC CCA GGC GCT CAC GCG ATG TGG CCG AGG     1641
Thr Ser Ala Pro Gly Thr Ser Pro Gly Ala His Ala Met Trp Pro Arg
                520                 525                 530
GCA GCT ACG CGC GCA TGC GCC ACC CCA TCG GGC TGC GGC TGC TGC AGC     1689
Ala Ala Thr Arg Ala Cys Ala Thr Pro Ser Gly Cys Gly Cys Cys Ser
            535                 540                 545
GGC GCC AGC AAG CGC GGC TCC ACG GTC ACG GCG CCC AAC GGC GCC AAG     1737
Gly Ala Ser Lys Arg Gly Ser Thr Val Thr Ala Pro Asn Gly Ala Lys
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        550                 555                 560
ACC TTC CCG ACC AAG CGG CCC TGG ATG ATC AGC CAC TGACCGCGGA          1783
Thr Phe Pro Thr Lys Arg Pro Trp Met Ile Ser His
    565                 570                 575
CCCTGCGCCG CACCAATGAC AAGGGCCCGC GACGCGGGCC TTTGTCCTGC CTGGCCGTAC   1843
CGCTCAGTGC ACGGCGCCGA TGAAGCCGGC CAGCTCCGGC GTCTGCGGGT TGGCGAACAG   1903
CTGCTTGGCC CGGGGCCGCT TTCGTGGATC CCCGGTACCG AATCGATC               1951
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(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 575 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2

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  1               5                  10                  15
Glu Asp Pro Phe Phe Pro Thr Ala Ile Ala Arg Ser Thr Pro Trp Pro
             20                  25                  30
Glu Thr Leu Ile Lys Val Asp Leu Asn Gln Ser Pro Tyr Asp Asn Pro
         35                  40                  45
Gln Val His Asn Arg Trp His Pro Asp Ile Pro Met Ala Val Trp Val
     50                  55                  60
Glu Pro Gly Ala Glu Phe Lys Leu Glu Thr Tyr Asp Trp Thr Gly Gly
 65                  70                  75                  80
Ala Ile Lys Asn Asp Asp Ser Ala Glu Asp Val Arg Asp Val Asp Leu
                 85                  90                  95
Ser Thr Val His Phe Leu Ser Gly Pro Val Gly Val Lys Gly Ala Gln
            100                 105                 110
Pro Gly Asp Leu Leu Val Val Asp Leu Leu Asp Ile Gly Ala Arg Asp
        115                 120                 125
Asp Ser Leu Trp Gly Phe Asn Gly Phe Phe Ser Lys Gln Asn Gly Gly
    130                 135                 140
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Gly Phe Leu Asp Glu His Phe Pro Leu Ala Gln Lys Ser Ile Trp Asp
145                 150                 155                 160
Phe His Gly Met Phe Thr Lys Ser Arg His Ile Pro Gly Val Asn Phe
                165                 170                 175
Ala Gly Leu Ile His Pro Gly Leu Ile Gly Cys Leu Pro Asp Pro Lys
            180                 185                 190
Met Leu Ala Ser Trp Asn Glu Arg Glu Thr Gly Leu Ile Ala Thr Asp
        195                 200                 205
Pro Asp Arg Ile Pro Gly Leu Ala Asn Pro Pro Asn Ala Thr Thr Ala
    210                 215                 220
His Met Gly Gln Met Gln Gly Glu Ala Arg Asp Lys Ala Ala Ala Glu
225                 230                 235                 240
Gly Ala Arg Thr Val Pro Pro Arg Glu His Gly Gly Asn Cys Asp Ile
                245                 250                 255
Lys Asp Leu Ser Arg Gly Ser Arg Val Phe Phe Pro Val Tyr Val Asp
            260                 265                 270
Gly Ala Gly Leu Ser Val Gly Asp Leu His Phe Ser Gln Gly Asp Gly
        275                 280                 285
Glu Ile Thr Phe Trp Gly Pro Ile Glu Met Pro Gly Trp Val His Met
    290                 295                 300
Lys Val Ser Leu Ile Lys Gly Gly Met Ala Lys Tyr Gly Ile Lys Asn
305                 310                 315                 320
Pro Ile Phe Lys Pro Ser Pro Met Thr Pro Asn Tyr Gln Gly Leu Pro
                325                 330                 335
Asp Leu Arg Arg His Leu Gly Gly Arg Lys Gly Gln Ala Ala Leu Pro
            340                 345                 350
Gly Arg Asp Arg Gly Leu Pro Pro Gly Leu Pro Glu Arg His Arg Val
        355                 360                 365
Pro Glu Glu Ile Arg Leu Gln Arg Arg Pro Gly Leu Leu Ala Ala Gly
    370                 375                 380
His Gly Ala Arg Ala Gly Pro His Gln Arg Arg Gly Gly Arg Ala Gln
385                 390                 395                 400
Cys Leu Arg His Ala Val Ala Ala His Gly Asp Leu Arg Leu Arg His
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                405                 410                 415

Gln Ser His Gly Arg Gly Thr Thr Glu Asp His His Gly Arg Gly Gly

            420                 425                 430

Ser Ala His Arg Pro Gly Gln Val Ser Pro Ala Tyr Asp Thr Arg His

        435                 440                 445

Pro Pro Phe Ala Arg Gly Arg Pro Cys Pro Pro Met Thr Thr Thr Ala

    450                 455                 460

Pro His Ala Ala Ala Ser Thr Arg Cys Ala Ala Ser Arg Ser Ala Thr

465                 470                 475                 480

Ser Pro Arg Pro Ala Pro Ala Ala Arg Arg Pro Arg Pro Ala Ser Ser

                485                 490                 495

Ser Ala Arg Arg Ala Trp Pro Ala Pro Ala Pro Asn Ser Ala Ala Pro

            500                 505                 510

Thr Thr Pro Thr Ser Ala Pro Gly Thr Ser Pro Gly Ala His Ala Met

        515                 520                 525

Trp Pro Arg Ala Ala Thr Arg Ala Cys Ala Thr Pro Ser Gly Cys Gly

    530                 535                 540

Cys Cys Ser Gly Ala Ser Lys Arg Gly Ser Thr Val Thr Ala Pro Asn

545                 550                 555                 560

Gly Ala Lys Thr Phe Pro Thr Lys Arg Pro Trp Met Ile Ser His

                565                 570                 575
```

CLAIMS:

What is claimed is:

1. An isolated enzyme capable of hydrolysing an enantiomer of the bicyclic lactam, 2-azabicyclo[2.2.1]hept-5-en-3-one, the enzyme having a stability characterised by hydrolysis at an initial concentration of 100 g racemic lactam plus 300 ml buffer and continuing to at least 90% hydrolysis of the (+) lactam with less than 5% hydrolysis of the (-) lactam.

2. The enzyme according to claim 1, having the characteristic that hydrolysis occurs at said initial concentration and continues to more than 98% of the (+) lactam with less than 2% hydrolysis of the (-) lactam.

3. An isolated ezyned capable of hydrolysing an enantiomer of the bicyclic lactam, 2azabicyclo[2.2.1]hept-5-en-one, obtaible from Comamonas acidovorans.

4. The enzyme according to claim 3, obtainable from Comamonas acidovorans, NCIMB 40827.

5. An isolated enzyme comprising the amino acid sequence shown in SEQ ID NO:2, or a fragment of SEQ ID NO:2 that is enzymatically active, capable of hydrolysing an enantiomer of the bicyclic lactam, 2-azabicyclo[2.2.1]hept-5-en-3-one and having a stability characterized by hydrolysis at an initial concentration of 100 g racemic lactam plus 300 ml buffer and continuing to at least 90% hydrolysis of the (+) lactam with less than 5% hydrolysis of the (-) lactam.

6. The enzyme according to claim 1, in immobilised form.

7. The enzyme according to claim 3, in immobilised form.

8. The enzyme according to claim 5, in immobilised form.

CAPLUS COPYRIGHT 2002 ACS DUPLICATE 1

TI Whole cell catalyzed kinetic resolution of 6-**azabicyclo**[3.2.0]hept-3-en-7-one: synthesis of (-)-cispentacin (FR 109615)

AN 1992:79774 CAPLUS

DN 116:79774

TI Whole cell catalyzed kinetic resolution of 6-**azabicyclo**[3.2.0]hept-3-en-7-one: synthesis of (-)-cispentacin (FR 109615)

AU Evans, Chris; McCague, Ray; Roberts, Stanley M.; Sutherland, Alan G.; Wisdom, Richard

CS Enzymatix Ltd., Cambridge, CB4 4WE, UK

SO Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry (1972-1999) (1991), (9), 2276-7
CODEN: JCPRB4; ISSN: 0300-922X

DT Journal

LA English

AB Enantioselective hydrolysis of the β- **lactam** (±)-(I) using **Rhodococcus equi** provided (+)-I, a precursor of the antifungal agent cispentacin (II).

TI Whole cell catalyzed kinetic resolution of 6-**azabicyclo**[3.2.0]hept-3-en-7-one: synthesis of (-)-cispentacin (FR 109615)

AB Enantioselective hydrolysis of the β- **lactam** (±)-(I) using **Rhodococcus equi** provided (+)-I, a precursor of the antifungal agent cispentacin (II).

IT **Rhodococcus equi**
(azabicycloheptenone kinetic resolution with, in cispentacin synthesis)

IT 97911-48-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(hydrolysis of, enantioselective, with **Rhodococcus equi**, in cispentacin synthesis)

L3 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 2

TI Chemoenzymic synthesis of (-)-carbovir utilizing a whole cell catalyzed resolution of 2-**azabicyclo**[2.2.1]hept-5-en-3-one

AN 1991:7049 CAPLUS

DN 114:7049

TI Chemoenzymic synthesis of (-)-carbovir utilizing a whole cell catalyzed resolution of 2-**azabicyclo**[2.2.1]hept-5-en-3-one

AU Taylor, Steven J. C.; Sutherland, Alan G.; Lee, Carol; Wisdom, Richard; Thomas, Steve; Roberts, Stanley M.; Evans, Christopher

CS Enzymatix Ltd., Cambridge, CB4 4WE, UK

SO Journal of the Chemical Society, Chemical Communications (1990), (16), 1120-1
CODEN: JCCCAT; ISSN: 0022-4936

DT Journal

LA English

OS CASREACT 114:7049

AB The resolution of (±)-2-**azabicyclo**[2.2.1]hept-5-en-3-one (I), a versatile intermediate in the synthesis of carbocyclic nucleosides, is described. Both optical forms of the **lactam** I have been obtained in very high optical purity (>98% enantiomeric excess) in rapid, facile, large-scale biotransformation processes using whole cell catalysts, and the levorotatory enantiomer has been converted into (-)-carbovir.

TI Chemoenzymic synthesis of (-)-carbovir utilizing a whole cell catalyzed resolution of 2-**azabicyclo**[2.2.1]hept-5-en-3-one

AB The resolution of (±)-2-**azabicyclo**[2.2.1]hept-5-en-3-one (I), a versatile intermediate in the synthesis of carbocyclic nucleosides, is described. Both optical forms of the **lactam** I have been obtained in very high optical purity (>98% enantiomeric excess) in rapid, facile, large-scale biotransformation processes using whole cell catalysts, and the levorotatory enantiomer has been converted into (-)-carbovir.

IT Pseudomonas solanacearum
Rhodococcus equi

(resolution by, of racemic azabicycloheptenone)

L3 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2002 ACS
TI enantiomers of 6-**azabicyclo**[3.2.0]hept-3-en-7-one and 6-**azabicyclo**[3.2.0]heptan-7-one and a process for their preparation by enzymic resolution of the racemates
AN 1993:168892 CAPLUS
DN 118:168892
TI enantiomers of 6-**azabicyclo**[3.2.0]hept-3-en-7-one and 6-**azabicyclo**[3.2.0]heptan-7-one and a process for their preparation by enzymic resolution of the racemates
IN Evans, Christopher Thomas; Roberts, Stanley Michael; Sutherland, Alan Gordon
PA Chiros Ltd., UK
SO PCT Int. Appl., 10 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9218477	A1	19921029	WO 1992-GB731	19920421
	W: AU, CA, JP, US				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE				
	AU 9216697	A1	19921117	AU 1992-16697	19920421
PRAI	GB 1991-8384		19910419		
	WO 1992-GB731		19920421		

OS CASREACT 118:168892; MARPAT 118:168892
AB Title compds. were prepared by enzymic resolution Thus, racemic azabicycloheptenone I was treated with **Rhodococcus equi** NCIB 40213 (ENZA-1) to give (1R,5S)-I in 40% yield and 99% enantiomeric excess. (1R,5S)-I was reduced and hydrolyzed to give cis-pentacin.
TI enantiomers of 6-**azabicyclo**[3.2.0]hept-3-en-7-one and 6-**azabicyclo**[3.2.0]heptan-7-one and a process for their preparation by enzymic resolution of the racemates
AB Title compds. were prepared by enzymic resolution Thus, racemic azabicycloheptenone I was treated with **Rhodococcus equi** NCIB 40213 (ENZA-1) to give (1R,5S)-I in 40% yield and 99% enantiomeric excess. (1R,5S)-I was reduced and hydrolyzed to give cis-pentacin.
IT **Rhodococcus equi**
(enzymic resolution by, of azabicycloheptenone in cis-pentacin synthesis)
IT Asymmetric synthesis and induction
(of cispentacin from **azabicyclo**[3.2.0]heptenone)
IT Resolution
(enzymic, of racemic **azabicyclo**[3.2.0]heptanone as intermediate for cis-pentacin)
IT 97911-48-3, (+)-6-**Azabicyclo**[3.2.0]hept-3-en-7-one
RL: RCT (Reactant); RACT (Reactant or reagent)
(enzymic resolution of)
IT 39155-94-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and **lactam** hydrolysis of)
IT 146864-12-2P, (1S)-6-**Azabicyclo**[3.2.0]hept-3-en-7-one
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, by enzymic resolution of racemic **azabicyclo**[3.2.0]heptanone)
IT 39155-95-8P 122672-46-2P, Cispentacin
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, from **azabicyclo**[3.2.0]heptenone enantiomer)

=>

L4 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
RN 63838-48-2 REGISTRY
CN 6-Azabicyclo[3.2.0]hept-3-en-7-one (9CI) (CA INDEX NAME)
OTHER NAMES:
CN (+)-6-Azabicyclo[3.2.0]hept-3-en-7-one

```
          1   FILE BIOSIS
                1   FILE BIOTECHABS
                1   FILE BIOTECHDS
                3   FILE CAPLUS
                1   FILE SCISEARCH
L1               QUE RHODOCOCCUS (W) EQUI AND AZABICYCLO AND LACTAM
                 ---------

     FILE 'CAPLUS, BIOSIS, BIOTECHDS, SCISEARCH' ENTERED AT 08:54:47 ON 04 NOV
     2002
L2             6 S L1
L3             3 DUP REM L2 (3 DUPLICATES REMOVED)

     FILE 'REGISTRY' ENTERED AT 08:57:22 ON 04 NOV 2002
L4             1 S 97911-48-3/RN
                 SET NOTICE 1 DISPLAY
                 SET NOTICE LOGIN DISPLAY
L5             0 S RHODOCOCCUS (W) EQUI AND AZABICYCLO AND LACTAMLOG HOLD

=> log hold
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    23.10      43.61

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                     0.00      -1.86

 SESSION WILL BE HELD FOR 60 MINUTES
STN INTERNATIONAL SESSION SUSPENDED AT 09:03:34 ON 04 NOV 2002
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